

(19) World Intellectual Property Organization  
International Bureau



PCT

(43) International Publication Date  
24 November 2005 (24.11.2005)

(10) International Publication Number  
**WO 2005/110052 A3**

(51) International Patent Classification: **A61M 11/00.**  
15/00. 15/08. 16/00. A62B 7/00

(21) International Application Number:  
PCT/US2005/016428

(22) International Filing Date: 11 May 2005 (11.05.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/569.888 11 May 2004 (11.05.2004) US

(71) Applicant (for all designated States except US): **PULMONOX TECHNOLOGIES CORPORATION**  
[CA/CA]: 4231 Glenhaven Crescent, North Vancouver, British Columbia V7G 1B8 (CA).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **MURRAY, Bruce**  
[CA/CA]: P.O. Box 1020, 5243 53rd Avenue, Tofield, Alberta T0B 4J0 (CA). **PERRY, Bryan** [US/US]: 679

Laydecket Road, West Seneca, New York 14224 (US).  
**MULLER, Christopher** [CA/CA]: 4231 Glen Haven Crescent, North Vancouver, British Columbia V7C 1B8 (CA). **HOLE, Doug** [CA/CA]: 92 Valleyview Crescent, Edmonton, Alberta T5R 5T1 (CA).

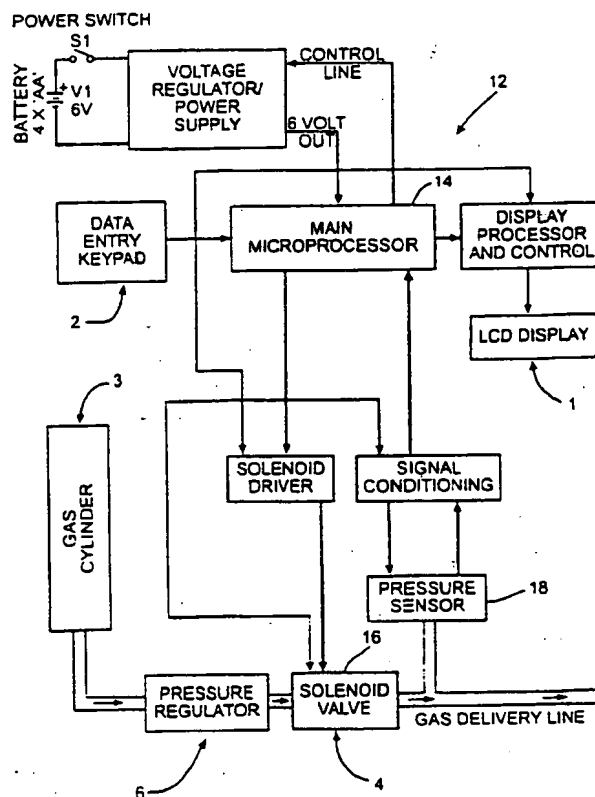
(74) Agents: **TENER, Carissa A.** et al.: Sidley Austin Brown and Wood LLP, 555 West Fifth Street, Los Angeles, California 90013 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,

[Continued on next page]

(54) Title: THE USE OF INHALED GASEOUS NITRIC OXIDE AS A MUCOLYTIC AGENT OR EXPECTORANT



(57) Abstract: Methods and devices for treating excess mucus accumulation in mammals by administering gaseous inhaled nitric oxide as a mucolytic agent or expectorant are provided. Delivery of gaseous nitric oxide can be made nasally or orally and is preferably substantially coincident with inhalation of the mammal or based on a synchronous parameter of the mammal's respiratory cycle. Varying therapeutic profiles may be used for the delivery of gaseous nitric oxide depending on the severity of the excess mucus accumulation. Parameters for the therapeutic profiles may include flow rate of nitric oxide containing gas, duration of administration of nitric oxide containing gas, number of breaths for which nitric oxide containing gas is to be administered, and concentrations of therapeutic NO delivered to the airways.



ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),  
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,  
FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO,  
SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN,  
GQ, GW, ML, MR, NE, SN, TD, TG).

(88) Date of publication of the international search report:  
2 March 2006

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

**Published:**

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

## THE USE OF INHALED GASEOUS NITRIC OXIDE AS A MUCOLYTIC AGENT OR EXPECTORANT

### FIELD OF THE INVENTION

5 [0001] The field of the present invention relates to methods and systems for treating, preventing, or mitigating mucus accumulation and mucociliary dyskinesia in the airways of mammals, and in particular, to the inhaled use of gaseous Nitric Oxide (gNO) for mucolysis.

### 10 BACKGROUND OF THE INVENTION

[0002] Mucus is comprised of high molecular weight proteins. It is a heterogeneous mix of primarily water, electrolytes, lipids, and proteins in a gel matrix. Goblet cells and submucosal glands that are located along the tracheobronchial tree produce it. Mucus is secreted in response to irritation of the airways and is elicited by  
15 viral, bacterial, and of major import, environmental contamination, primarily small particulates and allergens.

[0003] Airway hygiene and integrity also depends on mucociliary clearance (MCC), which in turn depends upon the movement of viscoelastic mucus along the tracheobronchial tree by the beating of the ciliary appendages of airway epithelial cells.  
20 However, because mucus secretions are viscous and thick, it is difficult for the ciliary appendages to move them, and excess accumulation further burdens the mucociliary functions. Conditions that encumber MCC result in an inflammatory response to the airway and increase the risk of colonization by microorganisms, such as pathogens, which if chronic, up regulate mucus production. Encumbered MCC may thus result in a  
25 vicious cycle of inflammatory damage with the potential for future damage to both the upper and lower airway. See e.g., Cole P., Minerva Anesthesiol. 2001 Apr; 67(4):206-9, "Pathophysiology and treatment of airway mucociliary clearance. A moving tale."  
Additionally, mucociliary dyskinesia, a condition of impaired mucociliary movement in the airways, is derived from a number of similar vectors, including environmental, and

likewise result in impaired mucociliary clearance times of respiratory secretions. See e.g., Pedersen M. Lung. 1990; 168 Suppl: 368-76, "Ciliary Activity and Pollution."

[0004] In equine mammals, for example, excessive mucus accumulation and the resulting inflammation prevalence may be present in as great as 33% of the population.

5 Excessive mucus accumulation is a significant risk factor for poor performance in racehorses. See e.g., S.J. Holcombe, N.E. Robinson, F.J. Derksen, et. al. 50th Annual Convention of the American Association of Equine Practitioners, 2004 (www.ivis.org) , 4-Dec-2004; P1441.1204, "Trachea Mucus Is Associated With Poor racing Performance In Thoroughbred Horses."

10 [0005] Furthermore, excessive mucus accumulation often manifests into Inflammatory Airway Disease (IAD). In humans, mucus accumulation also accompanies several respiratory diseases and conditions, such as acute bronchitis, chronic pulmonary disease, Bronchiectasis and Cystic Fibrosis.

[0006] Attempts at treating these airway derangements have focused on a wide  
15 range of interventions (antimicrobials, mucolytics, etc.) with limited success, particularly as it applies to the performance horse. Thus, there exists a need for more effective treatment methods for treating and preventing excess mucus accumulation and related pathology.

#### 20 SUMMARY OF INVENTION

[0007] The Applicants have unexpectedly found that gaseous NO when inhaled is an effective mucolytic agent that can break down thick mucus aiding in mucociliary clearance in the respiratory tract of mammals. Using an equine model as an example, the Applicants have demonstrated that the administration through inhalation of nitric oxide  
25 containing gas is an effective treatment of mucus accumulation, including the treatment of secondary mucociliary dyskinesia via increased mucociliary clearance in mammals. By breaking down the mucus to a less viscous liquid, mucociliary clearance is increased. Additionally, the administration of gNO further protects the respiratory airways from the vicious cycle of inflammatory damage and colonization by microbes because of its anti-

infective activity. Thus, gaseous nitric oxide (gNO) can be administered by inhalation as a novel methodology for reducing the severity and pathology of excess mucus residence in a mammal's respiratory airway, and in particular as an mucolytic agent or expectorant.

[0008] In one aspect of the present invention, mammals exhibiting excess mucus accumulation are identified and diagnosed. A source of gNO is provided, preferably in a pressurized cylinder coupled to flow control valves and pressure regulators. gNO may also be diluted with other gases such as N<sub>2</sub>, air, or O<sub>2</sub> to form a nitric oxide containing gas at a therapeutically effective amount of nitric oxide sufficient to reduce the presence of mucus in the mammal's airways by at least about 20%, preferably by at least about 50%, and more preferably by about at least about 75%. The nitric oxide containing gas is administered to the mammal, preferably through nasal delivery, but may also include oral delivery, for example, through a face mask or an endotracheal tube.

[0009] Preferably, the flow rate of gaseous nitric oxide is regulated dependent on the mammal's respiratory tidal volume and the administration is repeated over several breaths. The target concentration of nitric oxide in the mammal's airways preferably ranges from 80 ppm to 400 ppm, and more preferably 160 ppm to 220 ppm. The administration of the inhaled nitric oxide containing gas may also coincide with a synchronous parameter of the mammal's respiratory cycle.

[0010] Another aspect of the present invention includes prevention of excess mucus accumulation in a mammal's airway. Mammals that are at risk of excess mucus accumulation may be identified and diagnosed. Therapeutic effective concentration of nitric oxide may then be nasally or orally administered in an amount sufficient to prevent excess mucus accumulation, inflammation, and eventually colonization by microbes.

[0011] In another aspect of the invention, apparatuses and systems for treating or preventing excess mucus accumulation in a mammal's airway are provided. For example, the system may comprise an endoscope for determining an amount of mucus accumulation in a mammal's airway using a scoring system such as a discrete scale of 0 to 5, representing the absence of mucus to high levels of mucus, respectively. A nitric

oxide delivery device may be provided that include a source of nitric oxide containing gas, preferably from a pressurized source of gaseous NO such as a canister or cylinder, and a delivery interface for interfacing with the mammal's mouth or nares. The nitric oxide delivery device is preferably controlled by a control unit such as a microprocessor-based computer or analog controller wherein, depending on the scoring input  
5 representing the level of mucus accumulation, a distinct gNO therapeutic profile is selected and delivered to the mammals. Such therapeutic profile may be pre-determined or may be programmed by the user. The control unit then controls a flow meter and/or a control valve that regulates the flow of nitric oxide containing gas, either diluted or  
10 flowing directly from the pressurized source of gaseous NO.

[0012] Preferably, the apparatus delivers a quantity of the nitric oxide containing gas by regulating the flow rate depending on the mammal's respiratory tidal volume for a selected number of breaths at a certain concentration for the inputted score.

[0013] In another aspect of the invention, an system for treating mucus  
15 accumulation and/or mucociliary dyskinesia is provided. The system may comprise a pressurized source (e.g., canister or cylinder) of nitric oxide containing gas and a visible label affixed to the container, wherein the label indicates that the nitric oxide containing gas is suitable as a mucolytic agent or expectorant for reducing mucus accumulation and/or treating mucociliary dyskinesia in a mammal's airway. The system may further  
20 comprise instructions for delivery of the nitric oxide containing gas and/or instructions for therapeutic amounts or dosages of nitric oxide. Preferably, the concentration of nitric oxide in the pressurized source ranges from about 160 ppm to about 400 ppm, but may also be in excess of that amount such as 800 ppm to 10,000 ppm that may need to be diluted with other gases before use.

[0014] In a preferred embodiment, the pressurized source of nitric oxide  
25 containing gas is portable and can be carried by the mammal prior to initiation of treatment. The pressurized source may also include a release valve for controllably releasing the nitric oxide containing gas into a channel, tube or nozzle adaptable to direct

the nitric oxide containing gas to a nostril or mouth of the mammal. The release valve can be actuated to release the nitric oxide containing gas.

### BRIEF DESCRIPTION OF THE DRAWINGS

- 5 [0015] FIG. 1 illustrates an electromechanical gas delivery device;  
[0016] FIG. 2 represents the device described in FIG. 1.  
[0017] FIG. 3 illustrates a method of delivery of the gas to a horse;  
[0018] FIG. 4 illustrates an overall delivery system;  
[0019] FIG. 5 illustrates a J-tube used in conjunction with the device to induce gas into  
10 the nostril of a horse.

### DETAILED DESCRIPTION OF THE INVENTION

[0020] Before the present compositions and methods are described, it is to be understood that this invention is not limited to the particular devices, compositions,  
15 methodologies or protocols described, as these may vary. It is also to be understood that the terminology used in the description is for the purpose of describing the particular versions or embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

[0021] Although any methods, devices, and materials similar or equivalent to  
20 those described herein can be used in the practice or testing of embodiments of the present invention, the preferred methods, devices, and materials are now described. All publications mentioned herein are incorporated by reference. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

25 [0022] As used herein, terms such as "subject," "patient," and "mammal" may be used interchangeable. As used herein, a mammal's "airway" or "airways" refer to any of the various parts of the respiratory tract through which air passes during breathing, including, but not limited to the lungs and the trachea. As used herein, "treating excess mucus accumulation" encompasses one or more of the following: reducing mucus

accumulation, preventing excess mucus accumulation, mitigating and/or preventing mucociliary dyskinesia, and increasing mucociliary transport in the airway. As used herein, "therapeutically effective amount" refers to an amount sufficient: (1) to increase mucociliary transport in the mammal's airway by about at least 50%; (2) to increase  
5 MMC in the mammal by at least about 50%; and/or (3) to reduce the presence of mucus in the mammal's airways by about at least 20%.

[0023] Using an equine model, the Applicants have demonstrated that the administration of gaseous NO to mammals exhibiting excess mucus accumulation is effective in the treatment thereof. Specifically, nitric oxide containing gas was inhaled  
10 by six (6) equine exhibiting excessive mucus accumulation, and immediately, within 10-30 minutes, non-viscous liquids starts to flow out of the horses' nares, resulting in reductions of mucus to trace levels in all subjects. While gaseous nitric oxide has been utilized in other therapeutic applications such as to treat pulmonary vasoconstrictions, pulmonary infections, it is believed that effectiveness of gaseous NO as a mucolytic  
15 agent in treating excess mucus accumulation is novel and unexpected.

[0024] Delivering exogenous nitric oxide gas is an ideal mucolytic therapy because gaseous NO diffuses readily and uniformly into the respiratory airway to reach the mucus. Once absorbed, its biological activity is limited by avid binding to hemoglobin, rendering its activity short lived. Nevertheless, the short duration of its  
20 activity is preferred because it limits the untoward side effects of other systemic agents or drugs.

[0025] In a preferred embodiment, the administration of gaseous nitric oxide is performed using a gated flow system, and the concentration of gNO is dilutionally derived based on the mammal's inspiratory phase of the respiratory cycle. To achieve an  
25 inspiratory nitric oxide concentration of 160-220 ppm, for example, the mammal may need to receive a pre-determined higher concentration of nitric oxide and therefore a derived fraction of the mammal's tidal volume. The tidal volume of the mammal may be measured and determined using techniques well known in the art. The required



flow/concentration (e.g. 160 or 220 ppm of nitric oxide) may then be calculated based on the mammal's tidal volume.

[0026] For example, a sample calculation for a horse having a tidal volume ( $V_t$ ) of 7 liters per breath is as follows. Target NO dose concentration is 200 ppm. Source tank NO concentration is 10,000 ppm. Therefore,  $0.02 \times 700$  (100 brs  $\times V_t$  7 liters) = 14  
5 ltrs. Duration of NO gas at Equine respiratory rate ( $r_r$ ) of 12 / min. = 8.3 mins. Total inspiratory time @ I:E ratio of 1:2 = 2.76 mins. Therefore NO gas flow needed @  $r_r$  of 12/min = 14 ltrs. / 2.76 = 5.07 ltrs/min.

[0027] The following example describes the manner and process of  
10 administration of gaseous nitric oxide to equines that reduces excess mucus accumulation and increases mucociliary clearance according to the present invention. The following example should not be construed as limiting.

#### EXAMPLE

15 [0028] Six (6) Thoroughbred racehorses at a major racing jurisdiction were quarantined for two weeks, and each horse had evidence of excessive mucus production as surveyed by clinical presentation and by endoscopic exam. The horses were isolated from each other and were being medicated daily in series with several broad-spectrum antimicrobials routinely employed for respiratory infections in Equids. The results  
20 before the administration with gaseous NO had been unremarkable. Further physical exam revealed all other systems were within normal limits. All six horses were included in the study using gaseous NO.

#### Intervention / Methods:

25 [0029] The horses were brought individually to the veterinary hospital barn for further evaluation over the course of five days. An fiberoptic endoscope was passed to the level of the bifurcation of the trachea (carina-airway) with images recorded on videotape. A scoring system was used to indicate the presence or absence of mucus, as well as its severity, if present. This scoring system has been described by Dixon et. al.,

"Equine Pulmonary Disease: Ancillary Diagnostic Findings," Equine Vet. Journal 27, 428-435, 1995, herein incorporated by reference in its entirety. A score of zero indicates the absence of mucus, while a score of 1 to 5 indicates increasing amounts of mucus observed endoscopically in the trachea. The attending Veterinarian conducting the examination did the scoring. All of the six horses scored 4 or higher before the initiation of the treatments.

[0030] Treatment intervention of inhaled gaseous Nitric Oxide was administered to all six horses during a five-day period. Five of the horses (#2 – #6) received 100 breaths of 10,000 ppm resulting in, based on pulmonary mechanics, a lung concentration of approximately 160 ppm. Horse #1 received 100 breaths of 5000 ppm resulting in 80 ppm on Day #1 and a second administration of 100 breaths of 10,000 ppm on Day #5. Horse #5 received 100 breaths of 10,000 ppm on Day #3 and a second administration of 100 breaths of 10,000 ppm on Day #4.

[0031] It was observed that immediately following the administration of gaseous NO to the horses that non-viscous liquids started to flow out of the nares of the horses. The liquids appear to be mucus that has been hydrolyzed and thinned, and Applicants postulate that gaseous NO hydrolyzes the mucus by breaking down disulfide bonds in the mucus gel matrix.

[0032] The method of the inhaled NO administration was uneventful to other physiological systems and no untoward side effects were observed. An outline of the treatment results is provided below in Table No. 1 (with scores when available). At Day #1, all subjects had a score of 4 or greater. On a day where a measurement and a treatment occur, such as Day #4 for Horse #5, the measurement was taken before the administration of the second dosage.

Table No. 1

	Day #1	Day #2	Day #3	Day #4	Day #5	Day #6
Horse #1	Tx, 5k	Clear(0)	25 % rtn.	NG	NG, Tx 10k	Trace (1)
Horse #2	Tx, 10k	Clear(0)	25 % rtn.	NG	NG	NA
Horse #3	NA	Tx, 10k	Clear(0)	NG	Trace (2)	NA
Horse #4	NA	NA	Tx, 10k	Clear (0)	25% rtn.	NA

Horse #5	NA	NA	Tx, 10k	Clear (0), Tx, 10k	Trace (2)	Trace (1)
Horse #6	NA	NA	NA	NA	Tx, 10k	Trace (2)

Legend:

NA = Not applicable, not available for review

NG = No change in status

5 25% rtn = A return of 25% of the previous amount of mucus (amount before administration of gNO), not scored

Tx, 5 k = A treatment using 100 breaths at 5000 ppm

Tx, 10k = A treatment using 100 breaths at 10,000 ppm

(0-2) = Numerical scoring system

10

[0033] Although, not scored for the horses in which 25% of the mucus returned (Horses # 2 and #4), a 75% reduction in mucus from Day #1 was observed in these horses. In Horses #1, #3, #5 and #6, a reduction in mucus scores of 4 and 5 to trace amounts (score 1 and 2) demonstrates a reduction of about 40% to about 80% of mucus present in the airways.

15

[0034] Preliminary experiments with bovine show similar effectiveness with mucus being hydrolyzed and excreted from the nares within 10-30 minutes. Anecdotal studies with human volunteers with cold show similar effectiveness. Thus, the Applicants believe that inhaled gaseous NO as an effective treatment to excess mucus accumulation in the airways of mammals.

20

[0035] It is believed that the observed reduction in the presence of mucus was through the immediate mucolytic activity of gNO in breaking down the mucus gel matrix. While the NO molecule has been studied for many purposes, it is believed that the use of inhaled gaseous NO as a suitable mucolytic therapy is novel. Once liquefied, the ciliary appendages in the respiratory epithelial cells may then more easily transport and move the mucus to clear the respiratory airway.

25

[0036] Moreover, delivery of gaseous NO may increase the local bioavailability of nitric oxide that may regulate and increase the ciliary beat frequency of the respiratory epithelial cells. This leads to further ameliorating of mucociliary dyskinesia with subsequent decreased mucociliary transit time. Further, because of the anti-infective

30

activity of gaseous NO, longer duration and treatment profiles may be beneficial in removing the microbes or virus that may be causing the excess mucus secretion and accumulation.

[0037] Determining the treatment eligibility of an individual may be based upon the clinical presentation of excessive mucus accumulation in the upper lower airway.

The excessive mucus accumulation may be observed with an endoscope. A therapeutic amount of nitric oxide containing gas may be administered to a mammal to reduce the amount of mucus in the airways by at least about 20%, preferably at least about 50%, and more preferably, at least about 75%. The scoring system described by Dixon et al. 1995 provides a qualitative measure of the presence or absence of mucus, using a scale of 0-5.

Thus, a therapeutic amount of nitric oxide containing gas inhaled by a subject may be effective in decreasing this mucus score by at least 1 point, or by about 20%. Other means of quantifying mucus in the airways are also possible.

[0038] Additionally, inhaled nitric oxide containing gas may act as a preventative measure in the accumulation of mucus in the airways. Mammals may be selected that exhibit a risk of mucus accumulation. Such a risk may be associated with recent infection and/or contact with other infected mammals. Preliminary experiments with healthy bovine show that delivery of inhaled gNO results in the prevention of mucus accumulation. Additionally, in the equine study, the delivery of gNO did not result in any irritation, inflammation or abnormal side effects. The delivery of inhaled nitric oxide containing gas may be administered to these risk mammals in order to prevent mucus accumulation in the airway. Effective therapeutic amounts may also refer to an amount sufficient to break down the viscoelastic mucus and increase mucociliary transport in the mammal's airway and to increase MMC in the mammal. Therefore, treating mucus accumulation in the airways of a mammal comprises reducing mucus accumulation, preventing mucus accumulation, reducing mucociliary dyskinesia, and/or preventing mucociliary dyskinesia.

— Examples of Delivery Methods and Devices

[0039] Various methods and devices may be used to administer a therapeutically effective amount of nitric oxide containing gas to a mammal's airways. While preferred examples are provided herein, they are not intended to be limiting.

5 [0040] Effective therapeutics may include an administration of nitric oxide containing gas in a defined concentration of parts per million for a finite duration. Preferably, the target concentration of nitric oxide mammal's airways ranges from about 80 ppm to 400 ppm, and more preferably from about 160 ppm to about 220 ppm.

[0041] Delivery of nitric oxide gas to the airway may be achieved through  
10 delivery that coincides with the inhalation of the subject. In one embodiment for use with humans, gNO may be contained within portable pressurized canisters such as those used with portable inhalers that are well known in the art. Examples of inhaler designs are discussed in, for example, U.S. Pat. Nos. 5,823,180; 5,570,683; 4,667,668; 4,592,348; 4,534,343; and 4,852,561, each of which patents is herein incorporated by  
15 reference. Other inhaler designs are described in the Physicians' Desk Reference, 45th Edition, Edward R. Barnhart, Publisher (1991). Each of these and other aerosol-type inhalers can be adapted to accommodate the delivery of NO gas. This embodiment is especially suited for use by individuals suffering from, for example, common colds or allergy, congestive cough, and flu.

20 [0042] In use, the pressurized canister includes a release valve that can be manually actuated to controllably release gNO into a channel or tube adapted for insertion into the mouth or nostril of the mammal. Coincident with, or immediately before the inhalation by the mammal, the release valve can be actuated so as to release the gNO into the oral or nasal cavity and inhaled into the respiratory airway. Successive  
25 treatments and release of gNO coincident with the inspiration can be made depending on the therapeutic dosage. The amount of gNO release preferably ranges from about 0.5 ml to about 8 ml at a canister concentration of about 5000 or 10,000 ppm.

[0043] A visible label can also be affixed to the pressurized canister indicating

that gNO is used as a mucolytic agent to treat excess mucus accumulation or as an expectorant. Additionally, the pressurized canister can be included in a kit that also includes instruction for its use to treat excess mucus accumulation in the airway.

Preferably, the instruction instructs the user that exhibits excess mucus accumulation to insert the channel into his mouth or nostril and to actuate the release valve substantially coincident with the inhalation by the user.

[0044] In another embodiment envisioned for use in a hospital or clinical setting, breathable air from any source (e.g., ambient room air or ventilator carrying oxygen containing gas) may be directed to a nasal interface using techniques well known in the art. The inspiration and expiration flow rates of a spontaneous breathing of a mammal may be monitored using a flow sensor or flow meter known in the art and, inspiration flow profiles can be determined for the mammal's breathing. Inspiration flow profile of the breathable gas is the flow rate of the gas as a function of inspiration time. Delivery of the NO containing gas, preferably added to the breathable gas stream through a Y-piece connector, may be timed to coincide with the mammal's inspiration.

[0045] In the embodiments described to deliver the nitric oxide containing gas coincident with inspiration, the concentration of the gas delivered is dilutionally derived and is based on the individual's tidal volume. Thus, the final concentration of nitric oxide gas at the treatment site is a function of arbitrary flow rates and starting concentration. Accordingly, starting concentrations of gNO that are higher than the desired concentration for therapeutic effectiveness may be needed to account for the dilution by the breathable air flowing into the airway, and flow rates may be regulated flow rates may be regulated

[0046] For example, in humans, if the desired therapeutic concentrations of nitric oxide in the nitric oxide containing gas is about 160 ppm to about 220 ppm in the lungs, then the source gas may need to contain concentrations of nitric oxide of about 5000 ppm to about 10,000 ppm. In order to meet the therapeutic level in certain embodiments, a delivery concentration of the nitric oxide may need to be decreased by about 80-90

percent to account for dilution with breathable gas in a human patient. These values of nitric oxide containing gas may be delivered to a patient during their inspiration, wherein for example, a human patient is breathing at a flow rate of about 1 liter per minute.

Under this example, delivered nitric oxide containing gas having a concentration of about 5000 ppm at 1 liter per minute would be reduced to a concentration of about 65 ppm in the lungs when diluted by the breathable air. If the flow rate is changed to 2 liter per minute, then the delivered nitric oxide containing gas should have a concentration of about 5000 ppm to maintain the same concentration of about 130 ppm at the treatment site (therapeutic concentration). As another example, a pulse of about 1 to 1.5 seconds of nitric oxide would deliver 100 to 150 milliliters of nitric oxide into the airway and the lungs.

[0047] These calculations in humans may be recalculated using any concentration of source gas, using the tidal volume of human, which is about 0.5 mL per breath. If a source gas of 10,000 ppm is used and a target therapeutic concentration is 200 ppm, knowing that the tidal volume is 0.5 mL/bth, 1 liter of the gNO may be delivered over 100 breaths. A typical respiratory rate of a human is 12 bth/min, resulting in a treatment time of about 8.33 minutes. As another example, if a source gas of 10,000 ppm is used and a target therapeutic concentration is 100 ppm, about 0.5 liter of the gNO may be delivered over about 100 breaths. Calculations may be based on total minute ventilation of a patient, which is respiratory rate multiplied by tidal volume, for example is 0.5 L/bth x 12 bth/min = 6 L/min. An inspiratory ratio of 1:2 may be used with a human patient, resulting in a inspiratory time ratio of 0.33. A total inspiratory time per treatment may then be calculated multiplying the inspiratory time ratio by the treatment time, or 8.33 min x 0.33 = 2.78 min, in this example. An inspiratory gNO flow rate from device may be calculated by dividing the source gNO required per treatment by the total inspiratory time, or 0.5 L / 2.78 min = 0.18 L/min.

[0048] In the equine model, flow rates of nitric oxide containing gas will be greater than in the human model to account for greater tidal volume of the horse (about 7

liter per breath). However, horses take about the same number of breaths per minute as humans, about 12 per minute at rest. The flow values outlined below in Table No. 2 provide a guide that allows for effective delivery of near-optimal concentrations of the gas using a source cylinder concentration of 10,000 ppm of gaseous NO.

Table No. 2

Subject tidal volume Flow (7-8 ltrs)	Target Nitric Oxide Delivery (ppm)	NO Inspiratory Flow from device (100 brs.)
At rest	160	4.0 ltrs/min
At rest	200	5.07 ltrs/min

[0049] As alluded to above, the nitric oxide containing gas may be inhaled over a finite period of consecutive breaths. In equine, nitric oxide containing gas may be combined and delivered to about 100 consecutive nasal breaths. For example, using a 10,000 ppm nitric oxide gas source delivered coincident with the inspiratory flow of the horse in 100 breaths results in, based on pulmonary mechanics, a lung concentration of approximately 160 ppm. Using 5,000 ppm nitric oxide gas source in 100 breaths results in about 80 ppm.

[0050] With a source gas of 5000 ppm and a target therapeutic delivery concentration of 200 ppm, 28 liters of NO gas should be delivered over 100 breaths. The deliver treatments would delivered over 8.33 minutes. Total minute ventilation for a horse would be tidal volume (7 L/bth).multiplied by respiratory rate (12 bth/min), or 84 L/min. An inspiratory ratio of 1:2 may be used with a horse, resulting in a inspiratory time ratio of 0.33. A total inspiratory time per treatment may then be calculated multiplying the inspiratory time ratio by the treatment time, or 8.33 min x 0.33 = 2.78 min, in this example. An inspiratory gNO flow rate from device may be calculated by dividing the source gNO required per treatment by the total inspiratory time, or 28 L / 2.78 min = 10.08 L/min.

[0051] In yet another embodiment, triggering of the NO flow into the breathable



gas stream may also be accomplished by measuring and modeling the mammal's inspiration profile for a number of previous breaths. NO flow is then initiated on a subsequent breath based upon a predicted timing of the mammal's breathing to flow NO during inspiration. Yet another alternative method of determining the point to initiate the NO flow is by measuring the volume inspired by the mammal, which can be calculated based on the flow rate and elapsed time of flow of the breathable gas.

[0052] Those in the respiratory art, and particularly those familiar with ventilation methods, recognize the respiratory cycle of the mammal. The respiratory cycle is synchronous, defined by the inhalation and exhalation of the mammal. There are several synchronous parameters that may be observed to determine the inhalation and exhalation phases of the cycle. Examples of these parameters include the rate of flow of gas directed toward the mammal's airway, pressure change at the initiation of a breath, the synchronous movement of the laryngeal, and the synchronous motion of the chest wall. One or more of these parameters may be used as an indicator of the timing of mammal inhalation and exhalation. Thus, a synchronous parameter may be used to determine the initiation of a breath, and delivery of gNO may be timed according to the synchronous parameter to coincide with the inspiration of the mammal. This parameter may not be applicable to all mammals as anatomy will vary.

[0053] The above methods are preferably performed through the use of a control module, preferably a controller such as a computer microprocessor with associated logic (firmware or software), that may time the administering of the nitric oxide containing gas to the mammal's airway. The timing may be during the mammal's inspiration, at a predetermined or premeasured time. Alternatively, the mammal's inspiratory flow or volume may be measured and thus delivery will coincide with this measurement. This volume may be monitored or adjusted based on successive breaths.

[0054] In another embodiment, a pulse dose delivery or a bolus injection delivery of the NO containing gas may be used. The timing of the bolus injection may be correlated to the detection or observation of a mammal breath. For example, a bolus

injection of the NO containing gas may be delivered nasally or orally substantially coincident with the inhalation.

[0055] Systems and apparatus for delivery of nitric oxide containing gas have been described, for example, in U.S. Patent Application No. 10/315,539 (Publication No. 5 2003/0150457), which is herein incorporated by reference in its entirety. In that application, a nitric gas dispenser is described, which gates the flow rate of the gNO to the inspiratory phase of the respiratory cycle. The dispenser may also include a pressure sensor and a valve mechanism for controllably delivering the nitric oxide gas in connection with the subject's breathing. Synchronous inspiratory application may be 10 advantageous and necessary in order to quantify inhalant nitric oxide administration and minimize inadvertent human and/or mechanical error.

[0056] With reference to the FIGs., which describe a delivery method to a horse, FIG. 1 illustrates a block diagram representation of the device 12. With reference to FIG. 1, the device 12 has a power source 100. The power source can be an electrical outlet if 15 the user of the device is going to work out on a treadmill or a battery if the user will be working away from a confined environment like a track. The power source 100 provides sufficient voltage and charge to properly operate the device 12. The device 12 also has a controller that comprises main microprocessor 14 that controls the operation of a solenoid valve 16, also within the device 12. The solenoid valve 16 operates in 20 conjunction with operating parameters that are entered via a data entry keypad 2 and the input from a pressure sensor 18.

[0057] The operating parameters and the operating status of the device 12 are displayed on an LCD display 1. Along with the LCD display 1, the device 12 has a nitric oxide gas supply 3, preferably a cylinder. In that cylinder is nitric oxide having a 25 pressure of 1800 to 2200 pounds per square inch (psi).

[0058] The device 12 also has a pressure regulator 6. The pressure regulator 6 reduces the pressure of the nitric oxide to less than 100 psi so it can be administered to the mammal, such as a horse, without damaging the mammal's organs from too much

pressure.

[0059] Calibrating the flow through the solenoid valve 16 is obtained by selecting the pressure of the pressure regulator 6 and controlling the time that the solenoid valve 16 is open. Thereby, the valve 16 allows a precise amount of nitric oxide to be delivered through a gas delivery line 4, which delivers the nitric oxide to the mammal, preferably a horse. The pressure sensor 18 is designed to detect a drop in pressure in the gas delivery line 4, when the horse initiates a breath. This pressure drop signals the main processor 14 to open the solenoid valve 6 for a pre-programmed period of time. Among the parameters that are programmed into the device are: Total Breaths, Start Delay, Pulse Time, Pulse Delay, and Re-trigger Lock.

[0060] The programmable parameters are defined as follows:

[0061] Total Breaths: This parameter is the number of breaths programmed into a run. Each time a breath is detected as identified above, a pulse of nitric oxide gas is injected into the breath of mammal. Breaths that occur during a locked out time of the run are not counted as breaths. After the programmed number of breaths are counted, the run stops automatically and nitric oxide gas is no longer injected into any breaths of the mammal. This number can be set anywhere from 0 to 100 breaths. If the number is set at 0 then the auto shutoff is disabled and breaths will be injected with nitric oxide until the user stops the run.

[0062] Start Delay: This parameter is the programmed delay time in minutes that the user can set. The injection of nitric oxide gas into each breath will begin automatically after "Start Delay" minutes. It will then continue for the number of Total Breaths and then the device 12 stops automatically.

[0063] Pulse Time: This parameter is the length of time that the solenoid valve 16 will open for delivery of nitric oxide gas. The resolution is 0.1 seconds and the range is 0.1 sec to 0.9 seconds. If the regulator is set at 50 psi then each second of the solenoid valve 16 opening 31 cc of nitric oxide gas. If the regulator pressure is set at 30 psi then each 0.1 sec solenoid valve 16 opening represents 21 cc of nitric oxide gas. For example,

if the regulator is set at 50 psi and the pulse time is set at 0.3 seconds then each detected breath will be injected with a pulse of 0.3 seconds or about 90 cc of nitric oxide gas.

[0064] Pulse delay: This parameter is the length of time that the machine waits after detecting the beginning of a breath before opening the solenoid valve 16 to inject a pulse of nitric oxide gas. This allows the user to control the position of the bolus of nitric oxide gas in the breath. For example, if the user sets the solenoid valve 16 at 0.4 seconds, then 0.4 seconds after the beginning of the breath is detected the solenoid valve 16 will open to inject the nitric oxide pulse.

[0065] Retrigger Lock: This parameter is the total time that the machine will ignore new breaths beginning at the detection of a new breath. If this parameter is set at 4.5 seconds then the device 12 will wait, after detecting a breath, for 4.5 seconds before recognizing a new breath. Full or half breaths that are initiated by the animal during this lockout time will not be counted and no nitric oxide will be injected. If the breath is initiated before the lockout expires and the animal is still inhaling when the lockout expires then it will be recognized as a new breath and it will be counted and injected with nitric oxide.

[0066] With reference to FIG. 2, the data entry keypad 2 contains five active button switches defined as follows:

[0067] START/PULSE KEY 30: This key is used to start a run. The user is required to confirm the start by pressing an UP key 32 or to cancel by pressing a DOWN key 34. When a run is in progress, pressing this key will cause the run to pause. The run is then resumed by pressing the UP key 32 or stopping the run by pressing the DOWN key 34.

[0068] UP key 32: This key is used to confirm the start of the run, to resume a paused run and also to increment valve changes.

[0069] DOWN key 34: This key is used to cancel a started run, end a paused run and also to decrement valve changes.

[0070] NEXT key 36: This key is used to switch screen pages on the LCD display

1.

[0071] PURGE key 38: This key is used to open the solenoid valve 16 for two seconds to purge the line. This key is not active during a run. The LCD display 1 displays four screen pages, defined as follows:

5 [0072] Each screen page displays a status line. The status variations include NOT RUNNING, WAITING, RUNNING, PAUSED, PURGING and START Pressed.

[0073] The main screen page has a row of asterisks on the top line. This is the only screen available when the KEY switch is in the locked position. This screen displays the total breaths detected and also the total breaths that will cause the run to stop.

10 [0074] The second page shows two valves. The first is the START DELAY valve. When the screen first appears the blinking cursor shows the value, which can be changed by pressing either the UP or DOWN key. Pressing the NEXT key switches, the cursor to the second value on the screen which is TOTAL BREATHS.

[0075] The third page allows the user to change the PULSE DELAY and the  
15 PULSE TIME.

[0076] The fourth page allows the user to change the RETRIGGER LOCK.

[0077] With reference to FIG. 2, a capped port 5 is depicted. This is an alternate input port for nitric oxide and is utilized if the device is not used with the small gas cylinder as depicted in FIG. 2. The cap is typically replaced with a quick-connect style  
20 fitting for attachment to a standard regulators on a large gas cylinder.

[0078] In one embodiment, the controller may also comprise logic such as firmware or software for selection of a therapeutic profile for the administration of gaseous nitric oxide based on an input value representing a level of severity of mucus accumulation in the mammal's airway. The level of severity may be determined by an  
25 attending physician or veterinarian using, for example, a fiberoptic endoscope, as described in the study with horses. As an example, the input value may be 0, 1, 2, 3, 4, and 5, wherein 5 indicates a most severe condition of excess mucus accumulation, while 0 represents only a trace amount of mucus. It should be understood that there are many

variations on the types of input value, (e.g., A, B, C, et seq. or High Medium, Low, et seq., Most Severe, Severe, Medium, Trace, None), and these variations are considered as equivalents to a numerical scale.

[0079] The controller may further comprise a memory device such as a RAM, ROM, EPROM, hard disk, removable storage medium or other removable known in the art, wherein the memory device stores a number of therapeutic profiles each corresponding to a level of severity of mucus accumulation in the mammal's airways.

The therapeutic profiles can be pre-determined or programmable by the user. The parameters that make up the therapeutic profiles may include, but is not limited to, flow rate of nitric oxide containing gas, duration of administration of nitric oxide containing gas, number of breaths for which nitric oxide containing gas is to be administered, and concentration of therapeutic NO delivered to the airways.

[0080] In use, an attending physician or veterinarian makes a diagnosis of the severity of excess mucus accumulation in the mammalian's airway. The attending physician or veterinarian then input a value into the device 12 or select a value from a set of presented values by the device 12 via the data entry keypad 2. The device 12 via the controller is then instructed to execute the delivery of a certain therapeutic profile corresponding to the value inputted or selected. Table 3 illustrates a sample set of therapeutic profiles based on a nitric oxide gas source at 10,000 ppm for delivery to an equine. It should be understood that this example is not intended to be limiting, and other types of therapeutic profiles may be programmed into the device and delivered to the mammal.

Table No. 3  
Time Dose Profiling (10% reduction steps on No Breaths)

Input Value	flow rate	duration of administration	No. of breaths	Pre-Diagnosis
0				
1	4.0 ltrs./min	8.30 mins.	100 (160 ppm)	Mucus Score 1
2	5.07 ltrs./min	2.07mins.	25 (200 ppm)	Mucus Score 2

3	5.07 ltrs./min.	4.15mins.	50 (200 ppm)	Mucus Score 3
4	5.07 ltrs. min.	6.23 mins.	75 (200 ppm)	Mucus Score 4
5	5.07 ltrs/min	8.30 mins.	100 (200 ppm)	Mucus Score 5

[0081] FIG. 3 and 5 illustrate the method of delivering nitric oxide to the horse.

5 A J-tube 7 made of semi rigid plastic such as styrene is attached to the horses' halter 9 by two hook and loop fabric fasteners. A small clip 10 also secures the delivery line 11 to the halter 9. The delivery tube 11 is typically a clear plastic flexible tubing. The delivery line connects to port 4 shown in FIG. 2.

[0082] FIG. 4 shows a typical application in its complete form. The delivery  
10 device 12 is shown in a cradle 14 which attaches to a surcingle 13. This provides a convenient method of attaching the device to a horse.

[0083] Other delivery systems which may administer inhaled nitric oxide containing gas may include the delivery systems described in U.S. Patent No. 5,765,548, which is herein incorporated by reference in its entirety. As such, several delivery  
15 devices may nasally administer the inhaled nitric oxide containing gas. The devices may administer a therapeutic level of nitric oxide gas, such as an inhale nitric oxide containing gas having a concentration of about 160 ppm to about 220 ppm nitric oxide. One apparatus for treating mucus accumulation in a mammal's airway may include a transportable container comprising a nitric oxide containing gas, such as the transportable  
20 delivery device 12, attached to the subject in FIG. 4. The apparatus may also include a nozzle in fluid flow communication with the container, wherein the nozzle is operable to deliver the nitric oxide containing gas to one or both nostrils of a mammal. An example of the nozzle is the J-shaped nozzle 7 shown in FIG. 4 in fluid communication with the delivery device 12.

25 [0084] The apparatus may also include means including a flow meter for determining a physiological acceptable quantity of the nitric oxide containing gas to be delivered into the mammal's airway from the nozzle. Such a flow meter may be used to deliver nitric oxide containing gas having a concentration of about 160 ppm to about 220

ppm nitric oxide. The physiological acceptable quantity of the nitric oxide containing gas may correspond to the mammal's respiratory tidal volume, as described in the delivery mechanics described in FIGs. 1-4. The apparatus may also include an endoscope for determining the presence of mucus accumulation in the airway. This endoscope may communicate with the flow meter in order to deliver the nitric oxide containing gas when it detects a sufficient level of mucus accumulation.

[0085] In yet another embodiment of the invention, a kit or system may be provided for the treatment of mucus accumulation would comprise the a pressurized cylinder or canister containing gNO source and a label affixed to the cylinder or canister indicating that use of gNO as a mucolytic agent for the treatment of excess mucus accumulation.

[0086] Thus, a system may be assembled including a container comprising a nitric oxide containing gas and a visible label affixed to the container. The label may indicate that the nitric oxide containing gas is suitable for reducing mucus accumulation in a mammal's airway. Thus, a nitric oxide containing gas may be packaged and sold for the therapeutic use of reducing mucus accumulation in a mammal's airway. The label may also provide instructions for delivery of the nitric oxide containing gas and/or instructions for therapeutic treatments of mucus accumulation. As explained with reference to the human and equine models, the nitric oxide containing gas may have a concentration of about 160 ppm to about 10,000 ppm nitric oxide.

[0087] The example and figures describe the manner and process of nasal administration of gNO to an equine to reduce excess mucus accumulation according to the present invention. While embodiments of the present invention have been shown and described, various modifications may be made without departing from the scope of the invention. The invention, therefore, should not be limited, except to the following claims, and their equivalents.



### CLAIMS

1. A method of treating excess mucus accumulation in a mammal's airway comprising the steps of:  
providing a pressurized source of nitric oxide containing gas; and  
administering a therapeutically effective amount of nitric oxide containing gas to a mammal exhibiting excess mucus accumulation in the mammal's airway, wherein the nitric oxide containing gas is administered substantially coincident with the inspiration of the mammal.
2. The method of claim 1, further comprising the step of regulating a flow rate of the nitric oxide containing gas depending on the mammal's respiratory tidal volume.
3. The method of claim 2, wherein the concentration of nitric oxide containing gas in the mammal's airway ranges from about 160 ppm to about 220 ppm.
4. The method of claim 1, wherein the administration of the nitric oxide containing gas is timed according to a synchronous parameter of the mammal's respiratory cycle.
5. The method of claim 4, wherein the synchronous parameter is selected from a group consisting of rate of flow of gas directed toward the mammal's airway, pressure change at the initiation of a breath, the synchronous movement of the laryngeal, and the synchronous motion of the chest wall.
6. The method of claim 1, wherein the therapeutically effective amount of nitric oxide containing gas is sufficient to reduce an amount of mucus in the mammal's airways by at least about 50%.
7. The method of claim 1, wherein the therapeutically effective amount of nitric oxide containing gas is sufficient to effect mucolysis within thirty minutes.
8. A method of treating excess mucus accumulation in a mammal's airway comprising the steps of:  
identifying a mammal exhibiting excess mucus accumulation;  
determining the severity of mucus accumulation in the mammal;  
providing a source of nitric oxide containing gas;  
administering the nitric oxide containing gas using a distinct therapeutic profile corresponding to the severity of mucus accumulation in the mammal.

9. — The method of claim 8, wherein the severity of mucus accumulation is scored from 0 to 5, with 5 indicating a most severe condition.

10. The method of claim 8, wherein the distinct therapeutic profile is selected from a pre-determined set of therapeutic profiles.

11. The method of claim 10, wherein the distinct therapeutic profile comprises therapeutic parameters selected from a group consisting of flow rate of nitric oxide containing gas, duration of administration of nitric oxide containing gas, number of breaths for which nitric oxide containing gas is to be administered, and concentrations of therapeutic NO delivered to the airways.

12. A portable inhaler comprising:  
a pressurized canister comprising gaseous nitric oxide;  
a channel adapted for insertion into a mammal's mouth or nostril;  
a release valve for controllably releasing the gaseous nitric oxide into the channel; and  
a label indicating suitable use of gaseous nitric oxide as a mucolytic agent or expectorant.

13. A packaged kit comprising:  
the portable inhaler of claim 12; and  
an instruction sheet instructing a user having mucus accumulation to insert the channel into his mouth or nostril and to actuate the release valve substantially coincident with inhalation.

14. A nitric oxide delivery apparatus for treating excess mucus accumulation in a mammal's airway, the apparatus comprising:  
a source of gaseous nitric oxide;  
a delivery interface adapted to deliver gaseous nitric oxide to the mammal's airway;  
a flow control valve positioned downstream of the source of gaseous nitric oxide and upstream of the delivery interface; and  
a controller in communication with and controlling the flow control valve to regulate a flow rate of the gaseous nitric oxide from the source to the delivery interface; wherein the controller comprises logic for selection of a therapeutic profile of gaseous nitric oxide based on an input value representing a level of severity of mucus accumulation in the mammal's airway.

15. — The nitric oxide delivery apparatus of claim 14, wherein the controller further comprises a memory device that stores a number of therapeutic profiles of gaseous nitric oxide each corresponding to a level of severity of mucus accumulation in the mammal's airways.

16. The nitric oxide delivery apparatus of claim 14, wherein the input value is selected from a group consisting of 0, 1, 2, 3, 4, and 5.

17. The nitric oxide delivery apparatus of claim 15, wherein the therapeutic profiles are pre-determined and comprises therapeutic parameters selected from a group consisting of flow rate of nitric oxide containing gas, duration of administration of nitric oxide containing gas, number of breaths for which nitric oxide containing gas is to be administered, and concentrations of therapeutic NO delivered to the airways.

18. The nitric oxide delivery apparatus of claim 14, further comprising an input device for entering the input value into the controller.

19. An system for treating mucus accumulation, the system comprising:  
a pressurized cylinder comprising nitric oxide gas; and  
a visible label affixed to the container, wherein the label indicates that the nitric oxide containing gas is suitable as a mucolytic agent or expectorant.

20. The system of claim 19, further comprising an instruction sheet instructing delivery of nitric oxide gas from the pressurized cylinder to a mammal exhibiting excess mucus accumulation substantially coincident with inhalation of the mammal.

1/5

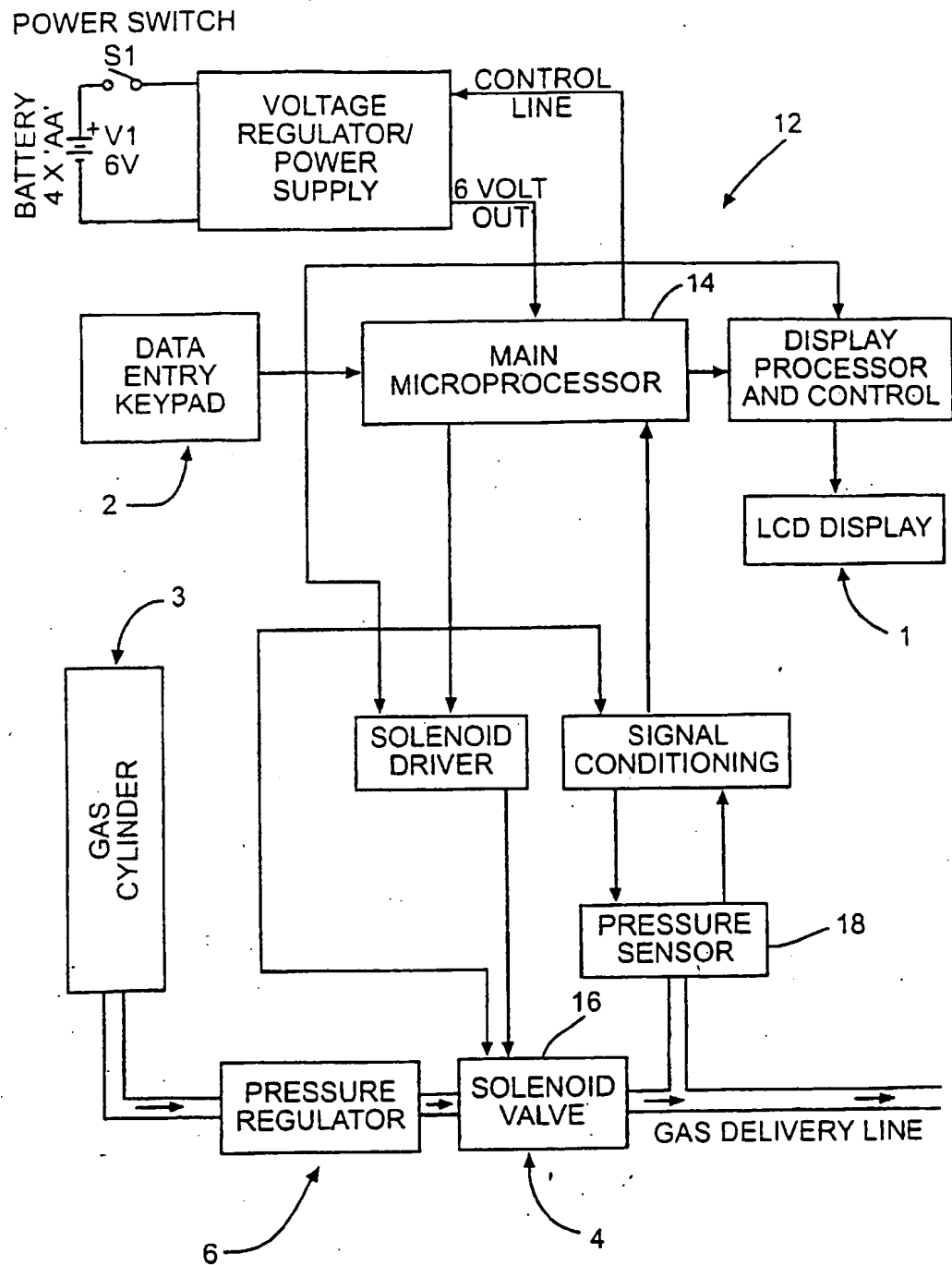


FIG. 1

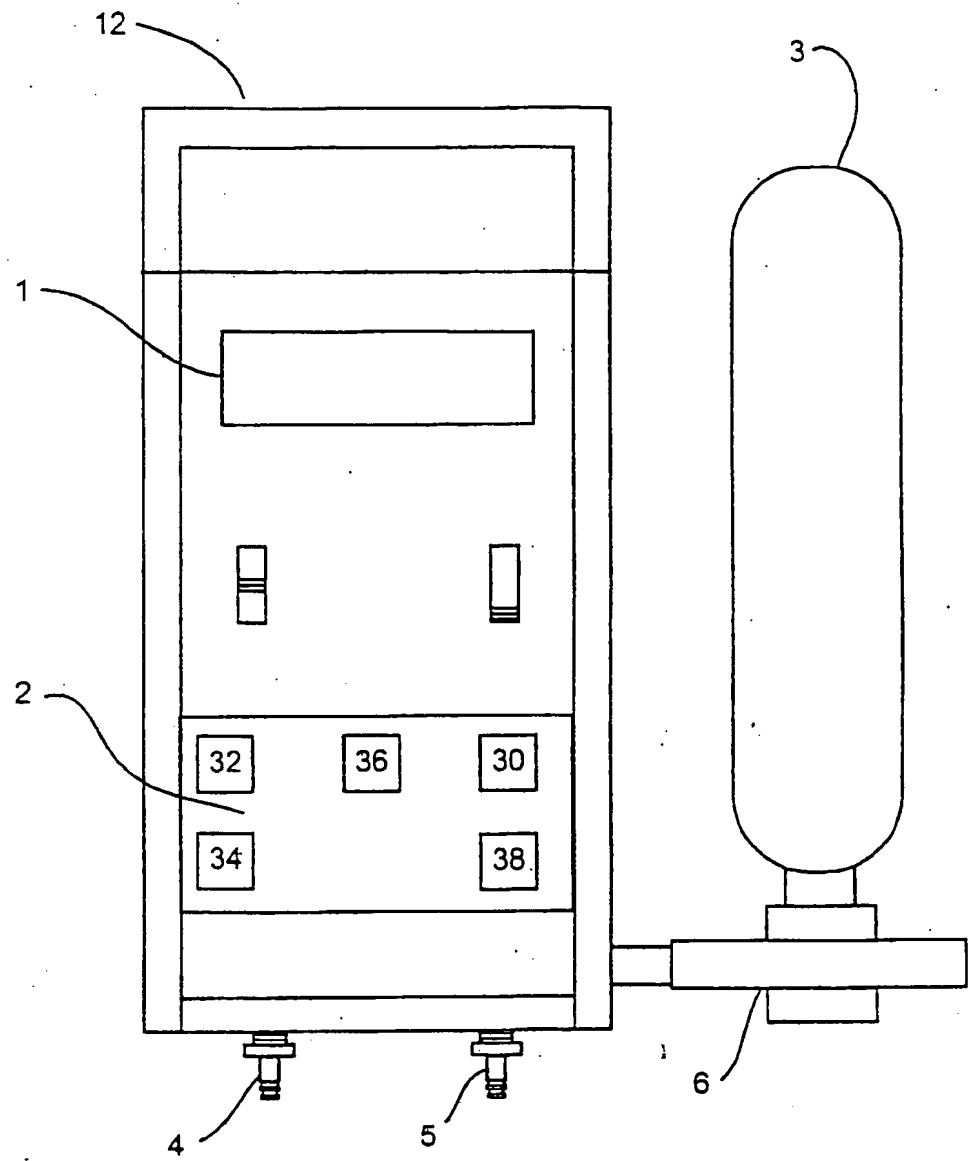


FIG. 2

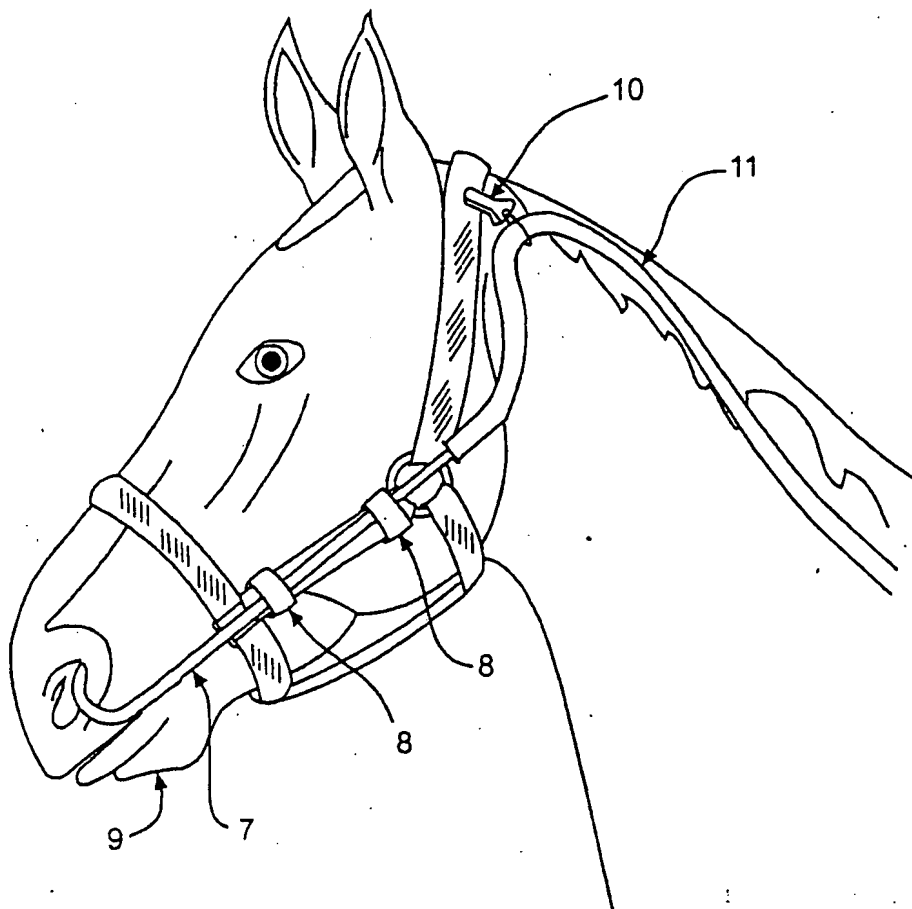


FIG. 3

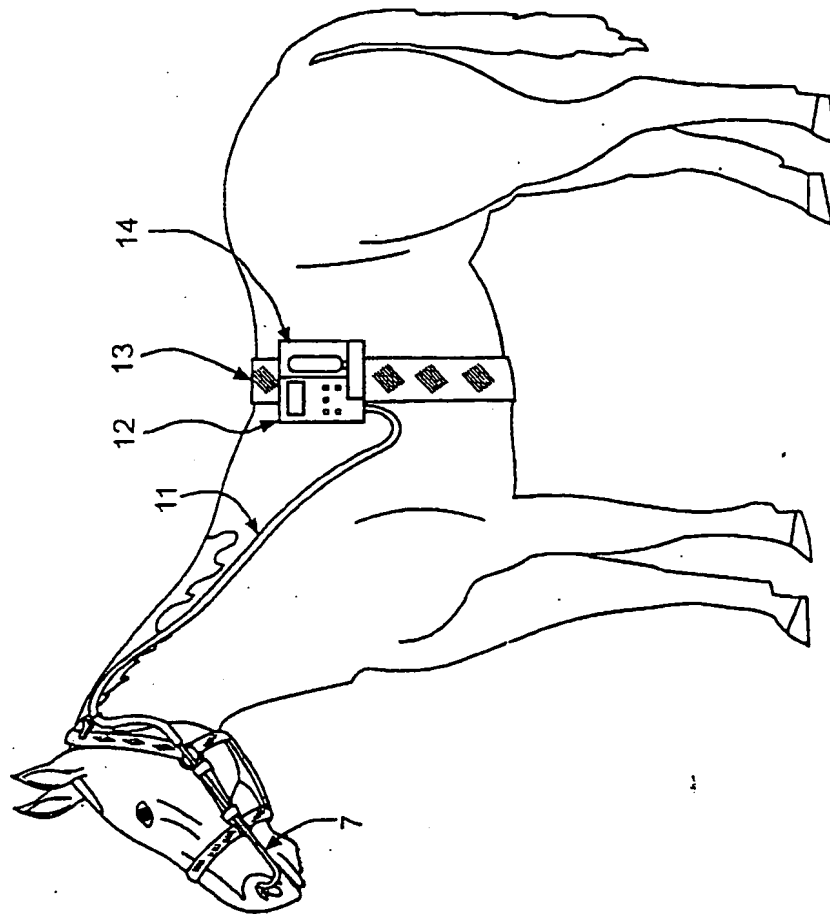


FIG. 4

5/5

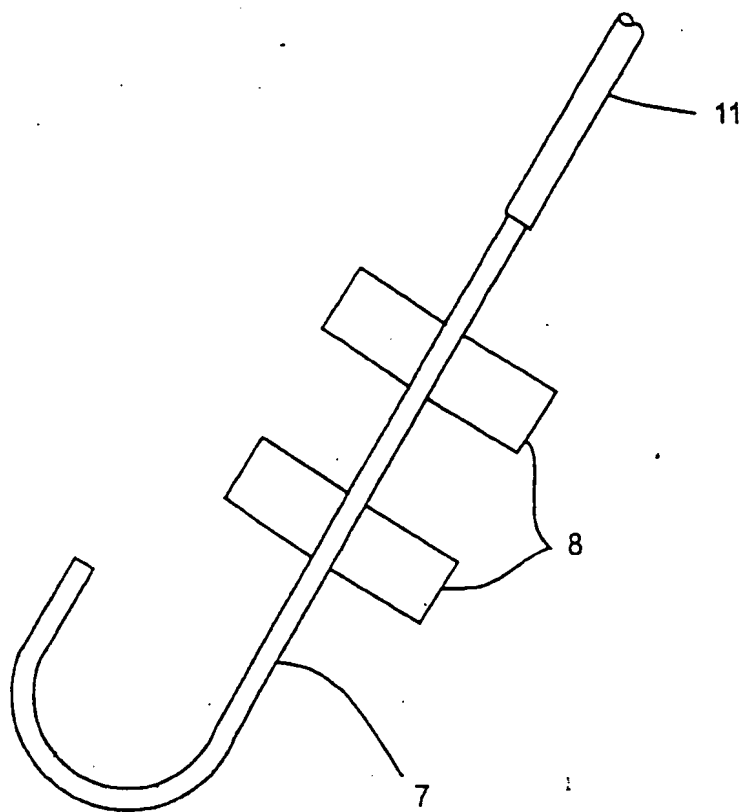


FIG. 5